REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the instant amendments and following remarks.

Claims 1-53, 55, and 59 are pending in the subject application. Claims 4, 10, 12, 14, 18, 34, 37, and 59 have been amended. Support for the amendments to the claims is found throughout the specification as filed and no new matter is presented by the amendments. For example, support for the amendments to claims 4 and 37 can be found at page 6, lines 12-13 and support for the amendments to claims 10, 12, 14, 18, and 59 can be found at page 16, lines 1-6. Claim 34 has been amended for grammatical consistency.

1. 35 U.S.C. §112, 2nd Paragraph Rejections

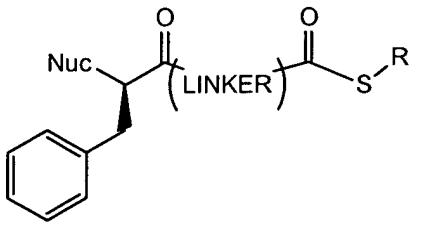
The Examiner has maintained the rejection to claims 4 and 37 under 35 U.S.C. § 112, second paragraph, as being indefinite because the term "weakly-nucleophilic" is unclear. Although Applicants continue to disagree with the position taken by the Examiner, the term "weakly nucleophilic" has been replaced in claims 4 and 37 with a listing of classes of weakly nucleophilic solvents identified in the specification at page 6, lines 12-13.

The Examiner has maintained the rejection of claims 10, 28-33, under 35 U.S.C. § 112, second paragraph, as being indefinite because the term "hydrocarbon group" is unclear. Although Applicants respectfully submit that the specification clearly defines the intended meaning of the term "hydrocarbon group," the claims reciting this term have been amended to replace the language "hydrocarbon group" with the language a "synthetic group comprising alkyl, cycloalkyl, alkenyl, alkynyl, aryl groups or a group that comprises a combination of two or more alkyl, cycloalkyl, alkenyl, alkynyl or aryl group regions and 0 to 3 heteroatoms selected from N, O, and S," which language is consistent with the definition of a "hydrocarbon group" provided at page 16, lines 1-6 of the specification.

Claims 12-33 stand rejected again under 35 U.S.C. § 112, second paragraph because the Examiner fails to see how "N-C_2-C_6alkanoylC_2-C_6aminoalkyl" is clear from the art and finds the "N" at the beginning of the name unclear.

The rejection is traversed.

The name "N-C_2-C_6alkanoylC_2-C_6aminoalkyl" is standard IUPAC nomenclature. The "N" defines the location of attachment of the C_2-C_6alkanoyl residue to the aminoalkyl residue. For example, claim 12 provides a substrate of the formula:



in which R is a N-C_2-C_6alkanoylC_2-C_6aminoalkyl group. Consistent with the IUPAC naming scheme and working from right to left, the sulfur atom of the substrate is attached to an amino substituted alkyl group having 2-6 carbon atoms, which amino residue is further substituted with an C_2-C_6alkanoyl residue (e.g., a (C_1-C_5alkyl-C(O)-residue). Thus, the term "N-C_2-C_6alkanoylC_2-C_6aminoalkyl" is clear and understandable to one of ordinary skill in the art.

Accordingly, the rejections to claims 1-55 and 59 under 35 U.S.C. § 112 should be deemed overcome and the claims found allowable.

2. 35 U.S.C. §112, 1st Paragraph Rejections

The Examiner has again maintained the rejection of claims 1-53, 55 and 59 under 35 U.S.C. 112 for containing subject matter which was not described in the specification. The Examiner asserts that although the specification provides an example of a cyclization reaction using tyrocidine A homologus series of polypeptide catalyzed by the thioesterase domain from the tyrocidine synthase, the claims are directed to a large genus encompassing different classes of organic compounds using

any thioesterase domain from any polyketide synthase gene cluster or any non-ribosomal peptide synthase. For example, the Examiner asserts that the majority of the substrates used in the cyclization reactions are short peptides (Table 1 at page 41), but that the few examples describing the use of peptide substrates does not support the claimed genus so that one of skill in the art would be able to predict the structure of the substrates usable in the claims. Applicants respectfully traverse the rejection.

Applicants again respectfully point out that it is the entire specification that is used to determine whether or not the written description requirement is met and not just the Examples disclosed in the specification. At page 6, line 17 to page 9, line 18 of the specification, other examples of substrates are given that fully describe and are commensurate with the scope of the claims. Not only are several examples given, they are described in terms of a generic structure, thus providing "common characteristics," i.e., structural, physical and chemical characteristics of the claimed substrates. That is, the generic structures of the substrates provide common chemical and structural characteristics that adequately describe the substrates.

In addition, the specification describes the substrates as having an "end group functionality of the natural substrate for the TE domain," thus describing the substrates functionally. Applicants respectfully note that the specification identifies ample excised TE domain proteins which are suitable for use in the macrocyclization methods of the claimed invention (See, for example, page 11, lines 16-23). Substrates for each of the identified TE domains provided by the specification are known such that homologous substrates suitable for macrocyclization by a specified excised TE domain can be readily rationally designed without undue experimentation based on the structurally variability provided by the instant specification.

Moreover, the specification provides amble working examples for a variety of substrates with a range of substitution from the wild-type substrates. For example, the specification provides macrocyclization methods in which excised tyrocidine A TE domain cyclizes substrates having substituted amino acids, depsi peptides, and synthetic (non-peptidic) residues inserted into the peptide chain. See, for example,

Table 1 on page 41, Table 2 on page 45, compounds 22-26 on pages 46-48. The specification also provides a working example for the preparation of macrocycle 28 from substrate 27 with an excised TE domain from surfactin S.

The claimed invention provides a chemical transformation in which a catalyst (the excised TE domain) cyclizes an acyclic substrate having an activated acyl residue and a nucleophile to form a macrocyclic product. The specification provides ample working examples of the claimed chemical transformation and teaches how to identify other catalysts (other TE domains) and substrates which are suitable for use with other catalysts.

Thus, one of skill in the art could predict the structure of a substrate useful in the claimed methods based on the teachings of the specification. Accordingly, claims 1-53, 55, and 59 are fully described and the specification meets the requirement of 35 U.S.C. 112.

Claims 34-53 and 55 remain rejected under 35 U.S.C. § 112, first paragraph because the Examiner asserts that although the genus of methods is discussed in the specification, there is no evidence that any representative species of such a large and varied genus, wherein the elongation step is repeated indefinitely, was in the possession of the inventors at the time of filing. The applicants respectfully traverse this rejection.

Claims 34 – 53 and 55 are not directed to methods wherein the elongation step is repeated indefinitely, by is repeated only "until the intermediate substrate is of sufficient length to undergo macrocyclization." The specification supports this at least at page 10, third paragraph to page 11, first carry over paragraph, where the specification describes that "[a]dditional elongation reactions can occur as needed until the substrate dimer molecule or oligomer is sufficiently long...," and "a pentapeptide substrate typically is not long enough to undergo macrocyclization." Additional support is provided at page 6, lines 3-6, which teach that macrocyclization substrates preferably generate cyclic compounds having between 4 and 20 amino acids or between 12 and 60 atoms in the ring. Dissociation of the TE domain bound pentapeptide occurs by

intermolecular nucleophilic attach of the N-terminal amine functional group form a second pentapeptide substrate to generate a decapeptide substrate dimmer that has a sufficiently long linear backbone for TE domain protein catalyzed macrocyclization...."

The elongation-cyclization methods of claim 34 is exemplified by the method of synthesis of gramicidin S from a pentapeptide precursor. See, page 45-46 and Fig. 3b-d. As provided in the specification, gramicidin S is a cyclic decapeptide formed by first dimerizing a pentapeptide to form a decapeptide which is subsequently cyclized to form a cyclic decapeptide.

Although the elongation/cyclization process is in competition with hydrolysis as noted by the Examiner, the specification clearly teaches how to select suitable substrates and provides evidence that the Applicant was in possession of the invention through the working examples.

Thus, additional elongation reactions are disclosed and enable the claims. Accordingly, claims 34 – 55 are fully described under 35 U.S.C. § 112, first paragraph.

Claims 1-55 and 59 remain rejected under 35 U.S.C. § 112, first paragraph for not reasonably providing enablement for methods using any PKS TE domains with any substrate or methods using NRPS TE domains with any substrate.

Applicants again respectfully traverse this rejection.

Applicants' specification is clearly enabled for the scope of the claims by disclosing multiple examples of TE domains appropriate to catalyze the macrocyclization reactions. There is no requirement that working examples be given for each and every embodiment. Applicants, however, provided evidence by the incorporation by reference of the Trauger, et al. reference, which is cited on page 11 of the specification. Trauger, et al. state that PKS systems can produce new polyketides and peptides. See page 216, 1st column of Trauger et al. In addition, as the specification states at the top of page 8, substrate specificity of other excised TE domains can be determined by those skilled in the art by routine procedures. Routine

procedures are not considered "undue experimentation" as the Examiner asserts. The Applicants then provide guidance to those skilled in the art as to how to select appropriate TE domains and their substrates. In addition, the specification provides many working examples of the claimed methods. Thus, under the Wands factors Applicants have fully enabled the scope of the claims because no undue experimentation is necessary, only routine procedures are needed to determine substrates; Applicants provide guidance in the specification as to how to choose TE domains and substrates; many working examples are presented; and those of skill in the art are considered highly skilled.

Accordingly, applicants request the withdrawal of these rejections and allowance of the claims.

3. 35 U.S.C. § 102 (a) Rejections

Claims 1-8 and 11 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Trauger *et al.* (Peptide cyclization catalyzed by the thioesterase domain of tyrocidine synthetase. Nature. Sept. 2000. 407:215-218). The Examiner considers Trauger *et al* to be "by others" because inventors Burkart and Schwarzer are not authors.

The Examiner has avered that "Trauger et al. is an admitted prior art in the specification, and support the enablemnet requirement, see page 11, second paragraph."

The Applicants submit herewith a copy of the Rule 131 Declaration filed with the previous response that effectively antedates the Trauger, et al., literature publication. Thus, Trauger, et al., is not available as prior art under 35 U.S.C. §102(a) against the claims of the instant application.

The Declaration under Rule 131 is sufficient to remove the Trauger reference from the prior art. As noted by the Examiner, Section 715(II)(G) states that:

> "[w] here applicant has clearly admitted on the record that subject mater relied on in the reference is prior art. In this case, that subject matter may be used as a basis for rejecting his or her claims and may not be overcome by an affidavit or declaration under 37 CRF 1.131."

However, the supporting case law has consistently required a clear admission that the reference is prior art. That is, the facts in each of the cited cases include a specific and definite admission that either (1) the inventive concept was the work of another or (2) the relevant reference was known at the time of filing.

In the instant case, no affirmative statement has been made by the Applicants. Moreover, as the office action is understood, the Examiner is attempting to improperly imply an admission from a mere discussion of the instant invention presented in certain portions of the specification. Thus, the Rule 1.131 declaration filed with the previous response **is** sufficient to remove Trauger from the available prior art. Accordingly, Applicants request withdrawal of the rejections and allowance of the claims.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

By _____

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